

# Risks in a Trial of an Innovative Treatment of Duchenne Muscular Dystrophy

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Studies of innovative therapies for muscular dystrophy raise unique ethical issues. The disease is currently untreatable and relentlessly progressive. A number of potentially efficacious treatments are being developed, but like all treatments, they may have unforeseen adverse effects. Nevertheless, patients and families, facing a bleak future, may be willing to take the gamble and try the treatments. Many doctors are eager to study them. But should institutional review boards approve them? This article discusses these issues and recounts the ways that one such study elicited different responses from different institutional review boards.

To protect minors from undue harm in clinical trials, a variety of protective measures exist in national and international legislation and ethical guidelines. Some measures are used worldwide, such as the requirements of proxy consent and ethical review. Other measures differ between countries. For example, some countries use the minimal risk threshold for nontherapeutic research; others do not.

The European Union (EU) offers a fascinating setting to consider the strengths and weaknesses of various protective measures, as within the EU the regulations vary. In 2001, the European Parliament and the Council of the European Union issued the Clinical Trials Directive to govern research involving human subjects.<sup>1</sup> This directive did not adopt a specific risk threshold for nontherapeutic research in children. In fact, it does not distinguish between therapeutic and nontherapeutic research at all.<sup>1</sup> Recently, a new regulation that will replace the current directive has been approved in the European Parliament. In this regulation, which is directly applicable in all EU member states, the regulation of risks

for pediatric clinical trials will be harmonized.<sup>2</sup> The 1997 Council of Europe's Convention on Human Rights and Biomedicine,<sup>3</sup> which is binding on only the European countries that have signed and ratified it, requires that nontherapeutic research in children entail no more than minimal risks and minimal burdens. By consequence, applicable regulation and corresponding review practices may vary among member states, and the risks in a single protocol may be assessed differently in different member states. Note that if a trial results in a market authorization for a new drug, it will cover the entire EU, including the member states in which the trial was rejected.

It is beyond dispute that minors should be protected against risks of harm when participating in research. A minimal risk threshold for nontherapeutic research can help protect minors in 2 ways. First, the threshold itself is a way of prohibiting studies that are deemed too risky. Second, the focus on nontherapeutic research can remind ethics committees that exposing children to risks and burdens solely for research reasons

## abstract

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requires adequate justification. The concept of minimal risk, however, is notoriously difficult to define precisely. Different definitions can lead to decisions about research protocols that might prevent breakthroughs for patients with urgent medical needs.

This Ethics Rounds discusses a 2008 trial in minor patients with Duchenne muscular dystrophy (DMD) that was approved in Belgium and Sweden but rejected in the Netherlands, where the law and review practices are more restrictive.

### THE CASE

In 2008, a Dutch research team submitted a protocol of a clinical trial investigating the safety, pharmacokinetics, and effects of subcutaneous injections of an antisense oligonucleotide (AON) in children with DMD for review in 3 EU member states simultaneously: Netherlands, Belgium, and Sweden.

The trial concerned a follow-up of a proof-of-concept study in the Netherlands, in which a single dose of PRO-051 (GSK-2402968, Drisapersen) was administered intramuscularly to 4 patients.<sup>4</sup> DMD patients would be eligible for the study if they were 5 to 16 years of age, had no evidence of dystrophin on previous diagnostic muscle biopsies, and had mutations that could be corrected by means of inducing exon 51 skipping, which might lead to dystrophin production in the muscles. The eligibility criteria also included an estimated life expectancy of  $\geq 6$  months, no serious preexisting medical conditions, and no respiratory insufficiency causing dependence on assisted ventilation. Concurrent treatment with glucocorticoids was allowed.

Children enrolled in the study would receive weekly abdominal subcutaneous injections of an AON (0.5 to 6 mg/kg body weight, with 3 patients receiving each dose) for

5 weeks. During that time, blood and urine samples would be collected for pharmacokinetic and safety measurements. Adverse events would be recorded. Efficacy would be assessed by measuring muscle strength, pulmonary function tests, and 2 or 3 muscle biopsies. No control group was included in the study; instead, each child's prestudy state would be the control. Six to 15 months after the final dose, all patients would enter a 12-week open-label extension phase, during which they all would receive the AON at a dose of 6.0 mg/kg per week.

The submitted protocol was approved in Belgium and Sweden. In the Netherlands, however, the reviewing ethics committee regarded the protocol as unacceptable and proposed major changes to the design of the trial. As a consequence, the researchers decided to conduct their study only in Belgium and Sweden. The different responses hinged on different ideas about the riskiness of the trial.

To support the discussion of the strengths and weaknesses of the different regulatory regimens that apply within the EU (and the appropriateness of the strategy chosen in the new European Clinical Trials Regulation recently approved in the European Parliament), we invited the principal investigator, a representative from each of the Dutch and Belgian reviewing committees, and a patient advocate to comment on this case. As a complement, *Pediatrics* assigned 2 independent professionals who were not involved in this case to discuss it further.

### Jan Verschuuren, Principle Investigator

The trial should have been approved for several reasons. First, the objectives were important: DMD is most frequently caused by a genetic defect that prevents the RNA from translating into protein and results in no (or only a trace amount of)

dystrophin in the muscles. The study was designed to show whether the administration of AON could restore the production of dystrophin protein. Second, although clinical trials should preferentially be conducted in adults who are capable of giving informed consent, the mode of action of the AON and the clinical features of DMD make it impossible to conduct a trial in adult patients with the disease. More specifically, the severe muscle loss that DMD patients develop over time makes it impossible to find a sufficiently large group of eligible adult patients. In addition, healthy volunteers would provide no alternative to adult patients, because the AON would actually cause DMD in healthy people.

Objections to the study focused on the unknown risks of AON. Because the risks could not be precisely quantified, they were deemed to be too high for a trial that involved children. This assessment ignores important features of DMD. The severity of DMD, its profound impact on the lives of the children and parents, its relentlessly progressive nature, and the fact that there is no treatment to modify the course of the disease make DMD a unique clinical problem. These features of the disease should be considered in weighing the risks of an experimental treatment against the risks of untreated disease. DMD patients may be willing to accept more risks and burdens than others would allow them to. That is not irrational. It must therefore be recognized that an objective risk standard may not do justice to this subjective experience of risks and burdens. Finally, the distinction between therapeutic and nontherapeutic (in Dutch law, described as research with or without a direct benefit to the research subject) may be arbitrary and unnecessarily block research. By definition, a clinical trial is not a therapy. The whole track from Phase I to Phase III clinical studies together, however, may potentially

result in therapy for the patient and the group. On this track, it is hard to define exactly where the therapeutic dimension begins.

#### **Monique Al and Gerard Koëter, Dutch Ethics Committee Members**

The Dutch Central Committee on Research with Humans (CCMO), a national ethics committee, reviewed both this study and the initial safety study to which this study was a follow-up.

With respect to the trial design, the follow-up study changed the mode of administration, the dosage, and the frequency of administration in comparison with the initial safety study. The CCMO judged that such a profound change could hinder correct interpretation of the data and considered the step from a singular intramuscular administration to a multiple subcutaneous administration unjustified. The committee recognized the importance of the trial, but preferred a more step-by-step approach in which PRO-051 would be administered to healthy adults first, to see whether it would reach the muscle after subcutaneous administration.

The CCMO also focused on the burdens of the research protocol. We judged them to be more than minimal. The protocol called for 12 hospital visits, including five 24-hour hospitalizations, a skin biopsy, 2 muscular biopsies, 12 blood samples, 2 insertions of a venous cannula, magnetic resonance imaging of the lower legs, many walking tests, muscle tests (including spirometry), and 5 subcutaneous injections. The CCMO suggested that the protocol would be more acceptable if fewer muscle biopsies were required.

Therefore, the committee proposed changes in the design leading to a lower burden in the investigated children. If these changes had been adopted by the researchers, the protocol could have been reconsidered by the CCMO.

#### **Elizabeth Vroom, Patient Representative**

The Duchenne Parent Project has been involved in the development of the antisense technique and the use of AON for DMD in the Netherlands since 1998. Our organization was very disappointed in the decision by the Dutch CCMO that led researchers to move their study of this novel technology to other European countries. Not having the protocol approved in the Netherlands made the Dutch Duchenne community miss out on the opportunity to build up experience with this new technology in the Netherlands. In addition, Dutch patients who could potentially benefit from this compound were prevented access to the trial compound, not only during the 4 weeks of the trial but also during the open-label extension trial that followed. In neighboring countries, research did enable therapeutic breakthroughs for which we are very grateful. We were disappointed, of course, that follow-up studies showed less success. We continue to work with regulatory agencies in Europe and the United States to see whether this approach to treatment can be approved.

We regret to have encountered several hurdles to having this trial take place in the Netherlands. First, in spite of plans to change it, Dutch law is stricter than in some other European countries, which made it more difficult to get approval for this trial. Second, we feel that some of the suggestions of the Dutch ethics committee were ethically questionable. For example, the suggestion to give the drug to healthy volunteers did not acknowledge prior work showing that, in healthy patients, the drug could cause harm by disrupting dystrophin production. In such situations, ethics committees need to ask the advice of external experts.

Most importantly, the ethics committee should have considered the opinions of patients and parents regarding risks and burdens of the treatment protocol.<sup>5</sup> After all, they are the ones

who take the burdens and the risks when participating. Many parents and patients would have been willing to participate. By not considering the viewpoints of patients and parents, the committee made it impossible for Dutch centers to participate in studies that were approved in other European countries.

#### **Walter van den Bogaert, Belgian Ethics Committee**

The Belgian law governing clinical trials and the protection of research subjects has specific requirements for trials in minors. In January 2008, this trial was accepted by the Ethical Committee of the University Hospital Leuven. The committee judged that the protocol was fully compliant with Belgian law. More specifically, the committee judged that the legal requirement of a “potential medical benefit” was met. It also assessed that appropriate measures had been taken to provide minor patients and their parents (or other legal representative) with correct and complete information. By consequence, no additional comments or inquiries were sent to the principal investigator.

#### **Matthew P. Meyer, Physiatrist**

For DMD, emerging therapeutics such as exon-skipping PRO-051, in addition to protein regulators, cellular therapies, and gene replacement therapies, offer the ability to treat the root causes of disease rather than merely the symptoms. In what would be an historic achievement, we may learn to slow, stop, or even reverse the course of this terrible, progressive genetic disease. To do so, however, it may be necessary to challenge accepted norms in pediatric research ethics. We may need to develop new ways to think about the how discoveries travel from bench to bedside.

The central question in new drug research is focused on whether it is acceptable to expose children to unknown and potentially great risks while testing drugs that may not have

any immediate benefits. In this case, the Dutch ethics committee is criticized for following established guidelines stipulating that research protocols must not be burdensome to pediatric participants and that the potential for harm must be firmly established from previous safety trials in adult subjects. By maintaining those standards, the research review board's decision clashes with the values of the parents and patients and ultimately obstructs potentially valuable clinical research for a vulnerable population of children. Parents, doctors, and ethicists all want to do what is best for children. But parents and doctors think that the best thing would be to accept research risks in the hope for a cure, whereas the ethicists maintain that risky research will be more harmful than beneficial for the child and should thus be restricted.

In scenarios such as this, there is a delicate balance between parental values, patient assent, and objective measures of risk and benefit. All of these must be considered and held in perspective by research ethics committees. As evidenced by the Dutch chapter of the international organization, Parent Project Muscular Dystrophy, families and patients are better informed and better connected with one another than ever before. As the ultimate stakeholders, members of this and other similar organizations for rare, serious, and life-limiting diseases may have more influence on the design and conduct of clinical trials than in the past. In situations such as muscular dystrophy, it will be harder and harder to maintain an inflexible framework of research ethics without taking into account the hopes of the patients and the burden of the disease on patients and families. It is my opinion that patients and families should be given a greater voice in the approval process for ethical research oversight. This needed change of the current standards will bring balance to the value of informed participation when risk cannot be completely avoided.

Without changes in current standards, we will not be able to do research on rare and fatal pediatric diseases. We will never be able to test potentially curative treatments.

Research ethics committees must allow higher-risk studies when a child faces a progressive disease for which treatment must be provided during childhood. The usual idea that research be done first in competent adults does not apply in these situations. The research must be done in children or it will not be done at all.

Children need to be protected from research risks. But the standard for judging those risks must be the risks associated with the child's underlying disease. Regulations should recognize that it may be quite rational for parents and patients to consent to clinical research on drugs that have never been tried in humans and thus that may have unforeseen and unforeseeable risks. Such research is best done in settings in which patients can be closely monitored, risks and benefits are carefully quantified, and safety monitoring boards do not allow studies to continue when there is evidence that they are not working. But the only way to know what will work and what will not is to allow responsible clinical research trials on important emerging therapeutics.

#### John D. Lantos

In most countries, laws and regulations governing biomedical research were developed without much input from the patients who would be the research subjects. In many cases, those patients (or their parents) are not very happy with the current regulatory systems. The most famous instance in which patients opposed the regulations (and ultimately changed them) was in the early days of research on treatments for AIDS. Today, many other patient groups are trying to change the rules that govern research. Research regulations should reflect the values and preferences of the people who

participate in research. This should not be a terribly radical suggestion. But current systems, in both the United States and Europe, often fail by these criteria. Research participants have little input into the choice of study questions, study design, data analysis, or publication of results. More importantly, they have little input into the regulations that will allow or prohibit their participation in studies. Perhaps it is time to change those regulations to better reflect the preferences of the research participants.

#### FURTHER DEVELOPMENTS

The study generated promising results that were published in the *New England Journal of Medicine*.<sup>4</sup> Follow-up research was initiated, and the AON was given a breakthrough therapy designation by the US Food and Drug Administration. Notwithstanding this impressive track record, it was recently announced that a Phase III placebo-controlled trial of Drisapersen did not show a clinically meaningful treatment difference between the active compound and the placebo for its primary endpoint, clinical relevant improvement including a 12-minute walking test. Researchers and the company that manufactures the drug plan further research with the compound.

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#### ABBREVIATIONS

AON: antisense oligonucleotide  
CCMO: Dutch Central Committee on Research with Humans  
DMD: Duchenne muscular dystrophy  
EU: European Union

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